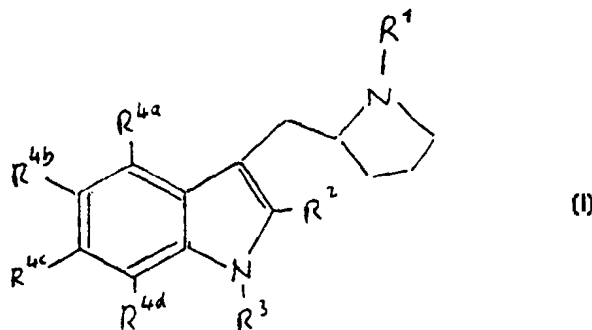




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07D 403/06, A61K 31/40, C07D 405/14, 409/14, 401/14</b>	<b>A1</b>	(11) International Publication Number: <b>WO 99/47516</b> (43) International Publication Date: 23 September 1999 (23.09.99)
(21) International Application Number: PCT/CA99/00222 (22) International Filing Date: 16 March 1999 (16.03.99) (30) Priority Data: 09/039,269 16 March 1998 (16.03.98) US (71)(72) Applicants and Inventors: SLASSI, Abdelmalik [CA/CA]; 3237 Cambourne Crescent, Mississauga, Ontario L5N 5G4 (CA). EDWARDS, Louise [CA/CA]; 35 Front Street, S. #2800, Mississauga, Ontario L5H 2C6 (CA). O'BRIEN, Anne [CA/CA]; 29 Glenlake Avenue, Upper Toronto, Ontario M6P 1W2 (CA). XIN, Tao [CN/CA]; Apartment 1211, 40 Fountainhead Road, North York, Ontario M3J 2V1 (CA). TEHIM, Ashok [IN/CA]; 7168 Sandhurst Drive, Mississauga, Ontario L5N 7H1 (CA). (74) Agents: HIRONS, Robert, G. et al.; Ridout & Maybee, 18th floor, 150 Metcalfe Street, Ottawa, Ontario K2P 1P1 (CA).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.

(54) Title: 3-(2-PYRROLIDINYL METHYL)-INDOLE COMPOUNDS HAVING 5-HT<sub>6</sub> AFFINITY

## (57) Abstract

Described herein are compounds with affinity for the 5-HT<sub>6</sub> receptor, which have general formula (I) wherein: R<sup>1</sup> is selected from the group consisting of H and C<sub>1-4</sub>alkyl; R<sup>2</sup> is selected from the group consisting of H, C<sub>1-4</sub>alkyl and benzyl; R<sup>3</sup> is selected from the group consisting of COR<sup>5</sup>, SO<sub>2</sub>R<sup>5</sup>, CONHC<sub>1-4</sub>alkyl and C(S)SR<sup>6</sup>; R<sup>4a</sup> is selected from the group consisting of H, OH, halo, C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy; R<sup>4b</sup> is selected from the group consisting of H, hydroxy, halo, C<sub>3-7</sub>cycloalkyloxy, C<sub>1-4</sub>alkoxy; C<sub>1-4</sub>alkyl, benzyloxy, phenoxy, trifluoromethyl, trifluoromethoxy and vinyl; R<sup>4c</sup> is selected from the group consisting of H, OH, halo, C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy; R<sup>4d</sup> is selected from the group consisting of H, OH, halo, C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy; R<sup>5</sup> is selected from the group consisting of phenyl, pyridyl, thienyl, quinolinyl and naphthyl which are optionally substituted with 1-4 substituents selected from C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkyl, halo, nitro, trifluoromethyl, trifluoromethoxy, 1,2-methylenedioxy, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkoxycarbonyl and C<sub>1-4</sub>alkylS-; and R<sup>6</sup> is selected from C<sub>1-4</sub>alkyl, allyl, propargyl and optionally substituted benzyl wherein the benzyl group is optionally substituted with 1-4 substituents selected from cyano, C<sub>1-4</sub>alkyl and halo. Also described is the use of these compounds as pharmaceuticals to treat indications where inhibition of the 5-HT<sub>6</sub> receptor is implicated, such as schizophrenia.

**FOR THE PURPOSES OF INFORMATION ONLY**

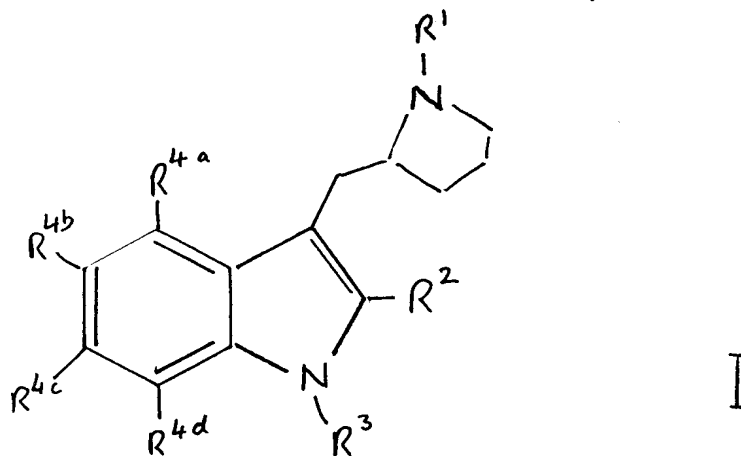
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

3-(2-PYRROLIDINYMETHYL)-INDOLE COMPOUNDS HAVING 5-HT<sub>6</sub> AFFINITY

This invention relates to indole compounds having affinity for the serotonin 5-HT<sub>6</sub> receptor, to pharmaceutical compositions containing them and to their medical use, particularly in the treatment of CNS conditions.

According to one aspect of the invention, there are provided compounds of Formula I and salts, solvates or hydrates thereof:



10

wherein:

R<sup>1</sup> is selected from the group consisting of H and C<sub>1-4</sub>alkyl;

R<sup>2</sup> is selected from the group consisting of H, C<sub>1-4</sub>alkyl and benzyl;

15 R<sup>3</sup> is selected from the group consisting of COR<sup>5</sup>, SO<sub>2</sub>R<sup>5</sup>, CONHC<sub>1-4</sub>alkyl and C(S)SR<sup>6</sup>;

R<sup>4a</sup> is selected from the group consisting of H, OH, halo, C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy;

20 R<sup>4b</sup> is selected from the group consisting of H, hydroxy, halo, C<sub>3-7</sub>cycloalkyloxy, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkyl, benzyloxy, phenoxy, trifluoromethyl, trifluoromethoxy and vinyl;

R<sup>4c</sup> is selected from the group consisting of H, OH, halo, C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy;

R<sup>4d</sup> is selected from the group consisting of H, OH, halo, C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy;

- 5 R<sup>5</sup> is selected from the group consisting of phenyl, pyridyl, thienyl, quinoliny and naphthyl which are optionally substituted with 1-4 substituents selected from C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkyl, halo, nitro, trifluoromethyl, trifluoromethoxy, 1,2-methylenedioxy, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkoxycarbonyl and C<sub>1-4</sub>alkylS-; and R<sup>6</sup> is selected from C<sub>1-4</sub>alkyl, allyl, propargyl and optionally substituted benzyl  
10 wherein the benzyl group is optionally substituted with 1-4 substituents selected from cyano, C<sub>1-4</sub>alkyl and halo.

According to another aspect of the invention, there is provided a pharmaceutical composition comprising a compound of Formula I in an amount  
15 effective to antagonize the 5-HT<sub>6</sub> receptor, and a pharmaceutically acceptable carrier.

In another aspect of the present invention there are provided compositions containing the present compounds in amounts for pharmaceutical  
20 use to treat CNS conditions where a 5-HT<sub>6</sub> ligand is indicated, for example, for the treatment or prevention of central nervous system disturbances such as psychosis, schizophrenia, manic depression, depression, neurological disturbances, memory disturbances, Parkinsonism, amyotrophic lateral sclerosis, Alzheimer's disease and Huntington's disease. These and other aspects of the present invention are  
25 described in greater detail hereinbelow.

#### Detailed Description and Preferred Embodiments

The term "C<sub>1-4</sub>alkyl" as used herein means straight and branched  
30 chain alkyl radicals containing from one to four carbon atoms and includes methyl, ethyl, propyl, isopropyl, t-butyl and the like.

The term "C<sub>1-4</sub>alkoxy" as used herein means straight and branched chain alkoxy radicals containing from one to four carbon atoms and includes methoxy, ethoxy, propyloxy, isopropyloxy, t-butoxy and the like.

5           The term "cycloalkyloxy" as used herein means saturated carbocycloxy radicals containing from 3-7 carbon atoms and includes cyclopropyloxy, cyclohexyloxy and the like.

10           The term "1,2-methylenedioxy" as used herein means "-O-CH<sub>2</sub>-O-" attached to adjacent nodes of a ring.

The term halo as used herein means halogen and includes fluoro, chloro, bromo and the like.

15           The term "pharmaceutically acceptable salt" means either an acid addition salt or a basic addition salt which is compatible with the treatment of patients.

20           A "pharmaceutically acceptable acid addition salt" is any non-toxic organic or inorganic acid addition salt of the base compounds represented by Formula I or any of its intermediates. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the  
25           mono-, di- and tricarboxylic acids. Illustrative of such acids are, for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicylic, 2-phenoxybenzoic, p-toluenesulfonic acid and other sulfonic acids such as methanesulfonic acid and 2-hydroxyethanesulfonic acid. Either the  
30           mono- or di-acid salts can be formed, and such salts can exist in either a hydrated, solvated or substantially anhydrous form. In general, the acid addition salts of

these compounds are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms.

5                   A "pharmaceutically acceptable basic addition salt" is any non-toxic organic or inorganic base addition salt of an acidic compound represented by Formula I or any of its intermediates. Illustrative inorganic bases which form suitable salts include lithium, sodium, potassium, calcium, magnesium or barium hydroxides. Illustrative organic bases which form suitable salts include aliphatic,  
10   alicyclic or aromatic organic amines such as methylamine, trimethyl amine and picoline or ammonia. The selection of the appropriate salt may be important so that an ester functionality elsewhere in the molecule is not hydrolyzed. The selection criteria for the appropriate salt will be known to one skilled in the art.

15                   "Solvate" means a compound of Formula I or the pharmaceutically acceptable salt of a compound of Formula I wherein molecules of a suitable solvent are incorporated in a crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered as the solvate. Examples of suitable solvents are ethanol and the like.

20                   The term "stereoisomers" is a general term for all isomers of the individual molecules that differ only in the orientation of their atoms in space. It includes mirror image isomers (enantiomers), geometric (cis/trans) isomers and isomers of compounds with more than one chiral centre that are not mirror images  
25   of one another (diastereomers).

                  The term "treat" or "treating" means to alleviate symptoms, eliminate the causation of the symptoms either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder or condition.

30                   The term "therapeutically effective amount" means an amount of the

compound which is effective in treating the named disorder or condition.

5 The term "pharmaceutically acceptable carrier" means a non-toxic solvent, dispersant, excipient, adjuvant or other material which is mixed with the active ingredient in order to permit the formation of a pharmaceutical composition, i.e., a dosage form capable of administration to the patient. One example of such a carrier is a pharmaceutically acceptable oil typically used for parenteral administration.

10 The term "schizophrenia" means schizophrenia, schizophreniform disorder, schizoaffective disorder and psychotic disorder wherein the term "psychotic" refers to delusions, prominent hallucinations, disorganized speech or disorganized or catatonic behavior. See Diagnostic and Statistical Manual of Mental Disorder, fourth edition, American Psychiatric Association, Washington, D.C.

15 The present invention includes within its scope prodrugs of the compounds of Formula I. In general, such prodrugs will be functional derivatives of the compounds of Formula I which are readily convertible *in vivo* into the required compound of Formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs" ed. H. Bundgaard, Elsevier, 1985.

20 In embodiments of the invention, compounds of Formula I include those in which R<sup>1</sup> is selected from H and C<sub>1-4</sub>alkyl. Preferably, R<sup>1</sup> is methyl. Also within the scope of the invention are compounds of Formula I wherein R<sup>2</sup> is selected from H, C<sub>1-4</sub>alkyl and benzyl. In preferred embodiments, R<sup>2</sup> is H.

30 Compounds of the invention include Formula I compounds wherein R<sup>3</sup> is selected from COR<sup>5</sup>, SO<sub>2</sub>R<sup>5</sup>, CONHC<sub>1-4</sub>alkyl and C(S)SR<sup>6</sup>. In preferred embodiments R<sup>3</sup> is selected from COR<sup>5</sup> and SO<sub>2</sub>R<sup>5</sup>. Within R<sup>3</sup>, R<sup>5</sup> is selected from

phenyl, pyridyl, thienyl, quinoliny and naphthyl which are optionally substituted with 1-4 substituents selected from C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkyl, halo, nitro, trifluoromethyl, trifluoromethoxy, 1,2-methylenedioxy, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkoxycarbonyl and C<sub>1-4</sub>alkylS- and R<sup>6</sup> is selected from C<sub>1-4</sub>alkyl, allyl, propargyl and optionally substituted benzyl wherein the benzyl group is optionally substituted with 1-4 substituents selected from cyano, C<sub>1-4</sub>alkyl and halo. Specifically, R<sup>5</sup> is selected from phenyl and thienyl optionally substituted with 1-3 groups selected from methyl, methoxy, fluoro, chloro and 1,2-methylenedioxy, and R<sup>6</sup> is selected from methyl, propargyl, benzyl and p-cyanobenzyl. In preferred embodiments, R<sup>5</sup> is selected from phenyl, p-methylphenyl, p-fluorophenyl, p-methoxyphenyl, o-chlorophenyl, o-methoxyphenyl, and thienyl and R<sup>6</sup> is methyl.

In further embodiments of the invention, R<sup>4b</sup> is selected from H, hydroxy, halo, C<sub>3-7</sub>cycloalkyloxy, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkyl, benzyloxy, phenoxy, trifluoromethyl, trifluoromethoxy and vinyl. In specific embodiments, R<sup>4b</sup> is selected from H, fluoro, cyclohexyloxy, hydroxy, benzyloxy, phenoxy, chloro, bromo and methyl. Preferably R<sup>4b</sup> is selected from chloro, cyclohexyloxy and fluoro.

In other embodiments of the invention, R<sup>4a</sup>, R<sup>4c</sup> and R<sup>4d</sup> are each independently selected from H, OH, halo, C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy. In a further embodiment, R<sup>4a</sup> and R<sup>4c</sup> are both H and R<sup>4d</sup> is halo. In a preferred embodiment, R<sup>4a</sup>, R<sup>4c</sup> and R<sup>4d</sup> are all H.

In embodiments of the invention, the compounds of Formula I include:

5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
2-Benzyl-5-hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
5-Hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
3-(1-Methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
1-(4-Methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;



- 5-Chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
5-Chloro-1-(4-methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-fluorophenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-Benzoyl-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5 1-(4-Methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(4-Fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(2-Chlorobenzoyl)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(2-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
10 5-Cyclohexyloxy-1-(3,4-methylenedioxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(2,6-dichlorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(2-thienoyl)indole;  
1-Benzoyl-5-bromo-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
15 1-Benzoyl-5-chloro-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-methylxanthyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-[S-(4-  
20 cyanobenzyl)xanthyl]indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-benzylxanthyl)indole;  
5-Methyl-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-methylxanthyl)indole;  
5-Fluoro-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-methylxanthyl)indole;  
1-(S-Benzylxanthyl)-5-fluoro-(1-methyl-2-pyrrolidinylmethyl)indole;  
25 1-(S-Allylxanthyl)-5-fluoro-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Fluoro-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-propargylxanthyl)indole;  
3-(1-Methyl-2-pyrrolidinylmethyl)-1-(S-methylxanthyl)indole;  
1-(S-Benzylxanthyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(S-Allylxanthyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
30 5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-benzoylindole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(4-

- methylphenylsulfonyl)indole;  
5-Benzyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(N-methylcarboxamido)indole;  
5-Hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(N-methylcarboxamido)indole;  
1-Phenylsulfonyl-5-hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)indole; and  
5 1-Phenylsulfonyl-5-phenoxy-3-(1-methyl-2-pyrrolidinylmethyl)indole.

In specific embodiments of the invention, the compounds of Formula I include:

- 10 5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
2-Benzyl-5-hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
5-Hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
3-(1-Methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
1-(4-Methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
15 5-Chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
5-Chloro-1-(4-methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-fluorophenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-Benzoyl-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(4-Methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
20 1-(4-Fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(2-Chlorobenzoyl)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(2-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(3,4-methylenedioxybenzoyl)-3-(1-methyl-2-  
25 pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(2,6-dichlorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(2-thienoyl)indole;  
1-Benzoyl-5-bromo-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-Benzoyl-5-chloro-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
30 5-Chloro-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;

- 5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-benzoylindole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(4-methylphenylsulfonyl)indole;  
1-Phenylsulfonyl-5-hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)indole; and  
5 1-Phenylsulfonyl-5-phenoxy-3-(1-methyl-2-pyrrolidinylmethyl)indole.

In more specific embodiments of the invention, the compounds of Formula I include:

- 10 5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
3-(1-Methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
1-(4-Methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
5-Chloro-1-(4-methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
15 5-Chloro-1-(4-fluorophenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-Benzoyl-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(4-Methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(4-Fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(2-Chlorobenzoyl)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
20 5-Cyclohexyloxy-1-(2-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(2-thienoyl)indole;  
1-Benzoyl-5-bromo-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-Benzoyl-5-chloro-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
25 5-Chloro-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-benzoylindole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(4-methylphenylsulfonyl)indole; and  
30 1-Phenylsulfonyl-5-phenoxy-3-(1-methyl-2-pyrrolidinylmethyl)indole.

In the most specific embodiments of the invention, the compounds of Formula I include:

- 1-(2-Chlorobenzoyl)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)indole;
- 5-Chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole; and
- 5-Chloro-1-(4-fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole.

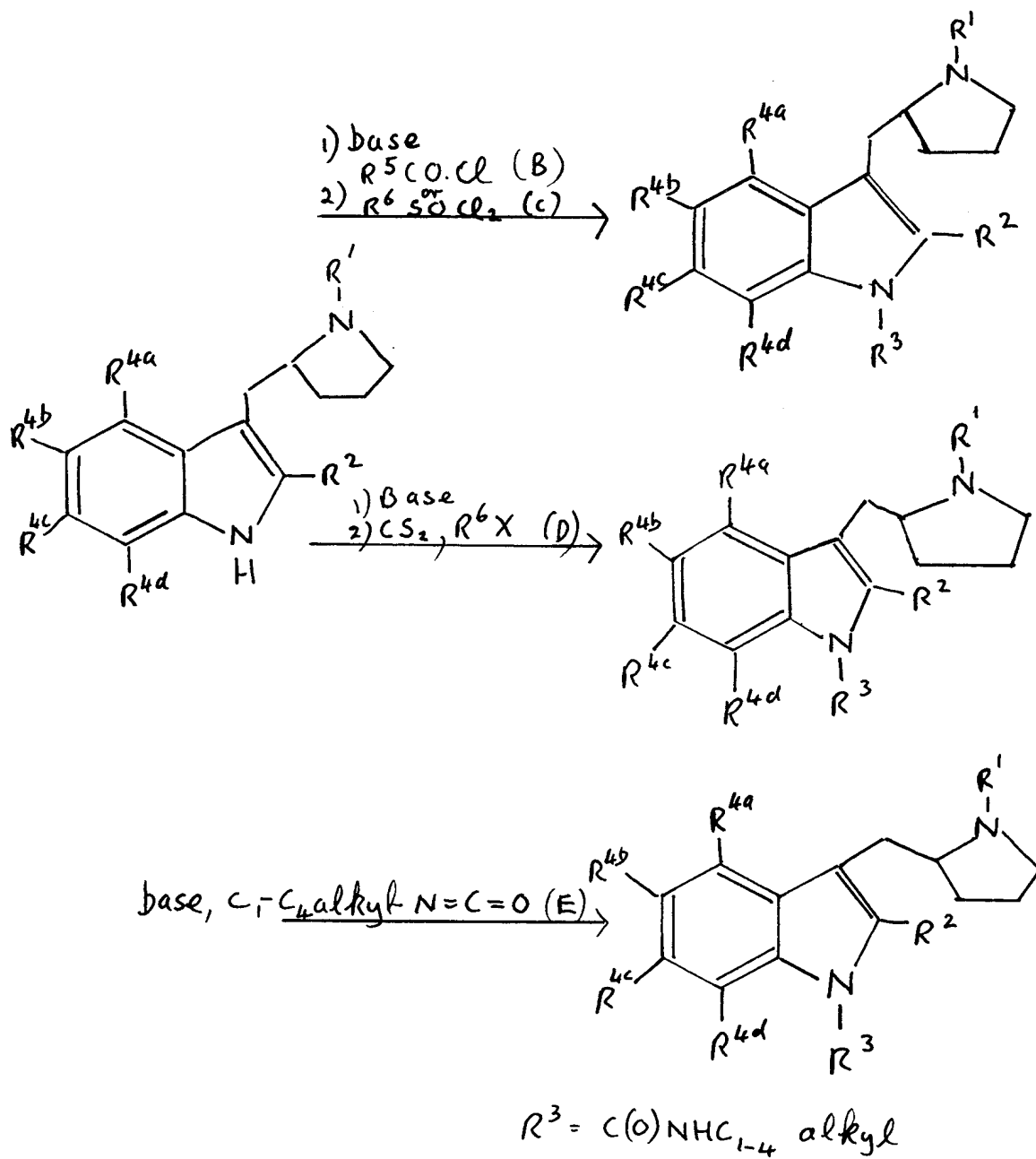
Acid addition salts of the compounds of Formula I are most suitably formed from pharmaceutically acceptable acids, and include for example those formed with inorganic acids e.g. hydrochloric, sulphuric or phosphoric acids and organic acids e.g. succinic, maleic, acetic or fumaric acid. Other non-pharmaceutically acceptable salts e.g. oxalates may be used for example in the isolation of compounds of Formula I for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt. Also included within the scope of the invention are solvates and hydrates of the invention.

The conversion of a given compound salt to a desired compound salt is achieved by applying standard techniques, in which an aqueous solution of the given salt is treated with a solution of base e.g. sodium carbonate or potassium hydroxide, to liberate the free base which is then extracted into an appropriate solvent, such as ether. The free base is then separated from the aqueous portion, dried, and treated with the requisite acid to give the desired salt.

All of the compounds of the present invention have at least one chiral centre. The invention extends to cover all structural and optical isomers of the various compounds, as well as racemic mixtures thereof.

In accordance with other aspects of the invention, the compounds of the present invention can be prepared by processes analogous to those established in the art. For example, as shown in Scheme 1, compounds of Formula I may be prepared by first treating compounds of Formula A, wherein R<sup>1</sup> is C<sub>1-4</sub>alkyl and R<sup>2</sup>

and  $R^{4a-d}$  are as defined in Formula I, with an appropriate base, followed by the addition of a reagent which will provide one of the various functional groups defined by  $R^3$  in Formula I. Therefore, for example, treatment of compounds of Formula A with a strong base such as lithium diisopropylamide, n-butyllithium or sodium bis(trimethylsilyl)amide in an inert solvent such as tetrahydrofuran or hexanes at a temperature in the range of -100 to 0 °C or, alternatively an organic amine in the presence of dimethylaminopyridine (DMAP), in an inert solvent such as methylene chloride or chloroform, at a temperature in the range of 0-60 °C, followed by the addition of acid chlorides of Formula B or sulfonyl chlorides of Formula C, wherein  $R^5$  is as defined in Formula I, provides compounds of Formula I wherein  $R^3$  is  $COR^5$  or  $SO_2R^5$  respectively. Preferred conditions are sodium bis(trimethylsilyl)amide in tetrahydrofuran at -78 °C followed by warming to room temperature or triethylamine and DMAP in methylene chloride at room temperature. In a similar fashion, compounds of Formula A can be treated with strong base such as lithium diisopropylamide, n-butyllithium or sodium bis(trimethylsilyl)amide, in an inert solvent such as tetrahydrofuran or hexanes, at a temperature in the range of -100-30 °C, followed by the addition carbon disulfide and then a reagent of Formula D, wherein X is an appropriate leaving group such as halo, preferably bromo or iodo, and  $R^6$  is as defined in Formula I, to provide compounds of Formula I wherein  $R^3$  is  $C(S)SR^6$ . Preferred reaction conditions include sodium bis(trimethylsilyl)amide in tetrahydrofuran at -78 °C followed by warming to room temperature. Compounds of Formula I wherein  $R^3$  is  $CONHC_1-4alkyl$  may be prepared by treating compounds of Formula A with a base such as triethylamine or potassium carbonate in the presence of isocyanates of Formula E in an inert solvent such as methylene chloride, acetonitrile, toluene or chloroform and at temperatures in the range of 0-120 °C. Preferred conditions include triethylamine in toluene at 110 °C. Reagents B, C, D and E are commercially available or can be prepared using standard methods known to those skilled in the art. The preparation of compounds of Formula A is described below.



Compounds of Formula I wherein R<sup>1</sup> is H may be prepared by treating a compound of Formula A, wherein R<sup>1</sup> is a suitable protecting group such as t-butoxycarbonyl (t-BOC), with reagents of Formula A, B, C, D (and CS<sub>2</sub>) and E as described above. Removal of the protecting group may be performed under standard conditions, for example using acidic conditions such as HCl in ethyl acetate to remove the t-BOC group, to provide compounds of Formula I wherein R<sup>1</sup> is H.

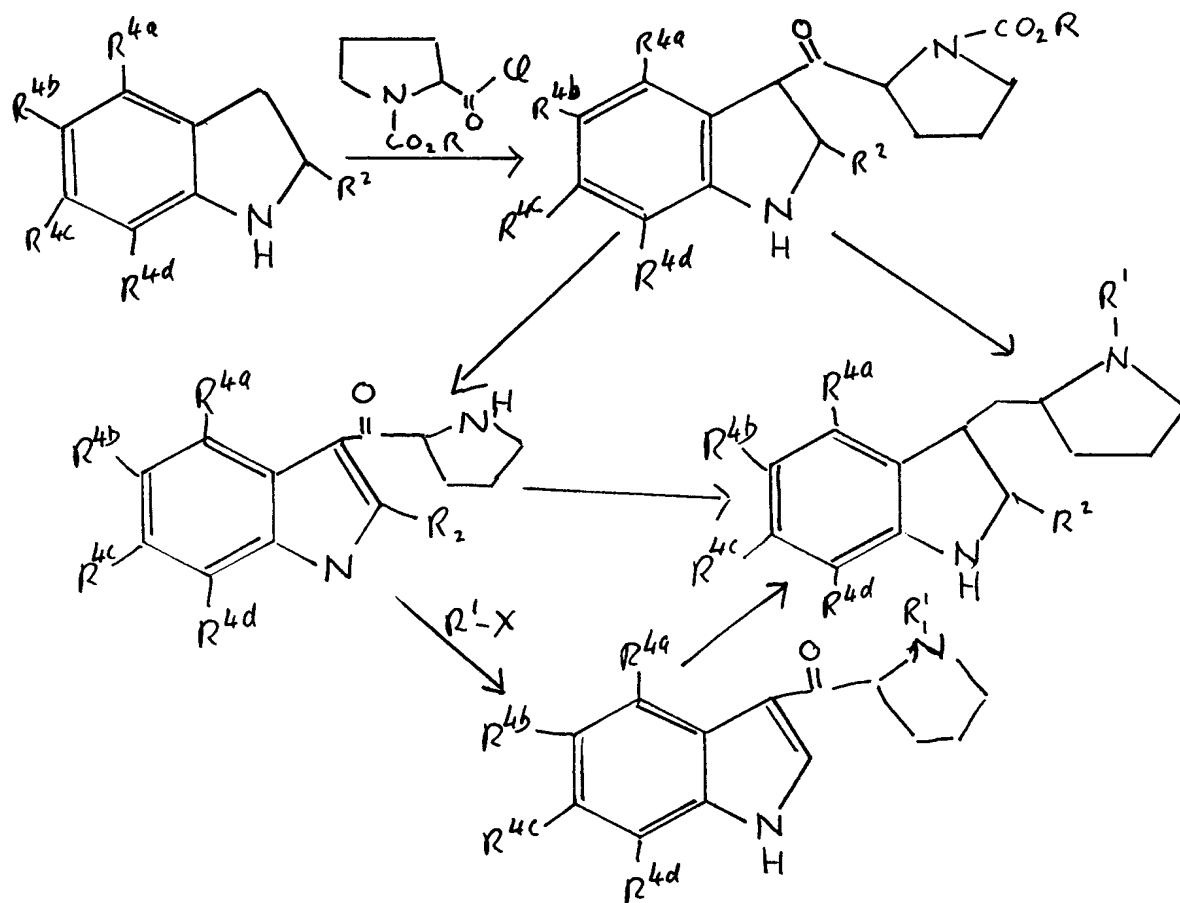
Compounds of Formula I, wherein R<sup>2</sup> is selected from C<sub>1-4</sub>alkyl and benzyl, R<sup>1</sup> is C<sub>1-4</sub>alkyl and R<sup>3</sup> and R<sup>4a-d</sup> are as defined in Formula I, may also be prepared by treating compounds of Formula I, wherein R<sup>2</sup> is H, R<sup>1</sup> is selected from C<sub>1-4</sub>alkyl and R<sup>3</sup> and R<sup>4a-d</sup> are as defined in Formula I, with a strong base, such as n-butyllithium, in an inert solvent, such as tetrahydrofuran, at a temperature in the range of -100-0 °C (preferably -78 °C), followed by the addition of a reagent of formula R<sup>2</sup>-X, wherein R<sup>2</sup> is selected from C<sub>1-4</sub>alkyl and benzyl and X is a suitable leaving group such as bromo, followed by warming to room temperature. The above reaction may also be carried out on a compound of Formula I, wherein R<sup>2</sup> is selected from C<sub>1-4</sub>alkyl and benzyl, R<sup>1</sup> is a suitable protecting group, such as t-butoxycarbonyl, and R<sup>3</sup> and R<sup>4a-d</sup> are as defined in Formula I, which, after removal of the protecting group using standard deprotection conditions (for example HCl in ethyl acetate to remove the t-butoxycarbonyl protecting group), provides a compound of Formula I wherein R<sup>2</sup> is selected from C<sub>1-4</sub>alkyl and benzyl, R<sup>1</sup> is H and R<sup>3</sup> and R<sup>4a-c</sup> are as defined in Formula I.

Compounds of Formula A wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>4a-d</sup> are as defined in Formula I may be prepared as shown in Scheme 2. Reagent F, in which R is, for example, benzyl, can be condensed with indole G, wherein R<sup>2</sup> and R<sup>4a-d</sup> are as defined in Formula I, typically by first converting the indole to a magnesium derivative by reaction with a suitable Grignard reagent, such as t-butyl- or ethyl-magnesium bromide, in an inert solvent. Then the magnesium derivative so formed can be reacted *in situ* with a reagent of Formula F to provide intermediates

of Formula H. Suitable solvents include tetrahydrofuran and diethylether (which is preferred). The reaction can be conducted at temperatures ranging from -30 to 65 °C, suitably at room temperature. Intermediate H may be reduced with hydride reducing agents to provide compounds of Formula A wherein R<sup>1</sup> is methyl. The preferred reducing conditions are lithium aluminum hydride in tetrahydrofuran at a temperature of around 65 °C. Alternatively, intermediate H may be deprotected under standard conditions, for example sodium hydroxide in methanol, to provide intermediates of Formula J. Intermediate J may then be alkylated on the pyrrolidine nitrogen by treatment with a reagent of the formula C<sub>2-4</sub>alkyl-X, wherein X is a suitable leaving group such as halogen, preferably bromo, in the presence of a mild base in an inert solvent to provide intermediates of Formula K. Suitable alkylation conditions include potassium carbonate in acetonitrile or triethylamine in dichloromethane. Temperatures may be in the range of 25 to 85 °C, preferably at room temperature. Intermediates J and K may be reduced with hydride reducing agents as described above to provide compounds of Formula A, wherein R<sup>1</sup> is H and C<sub>2-4</sub>alkyl respectively.

## Scheme 2



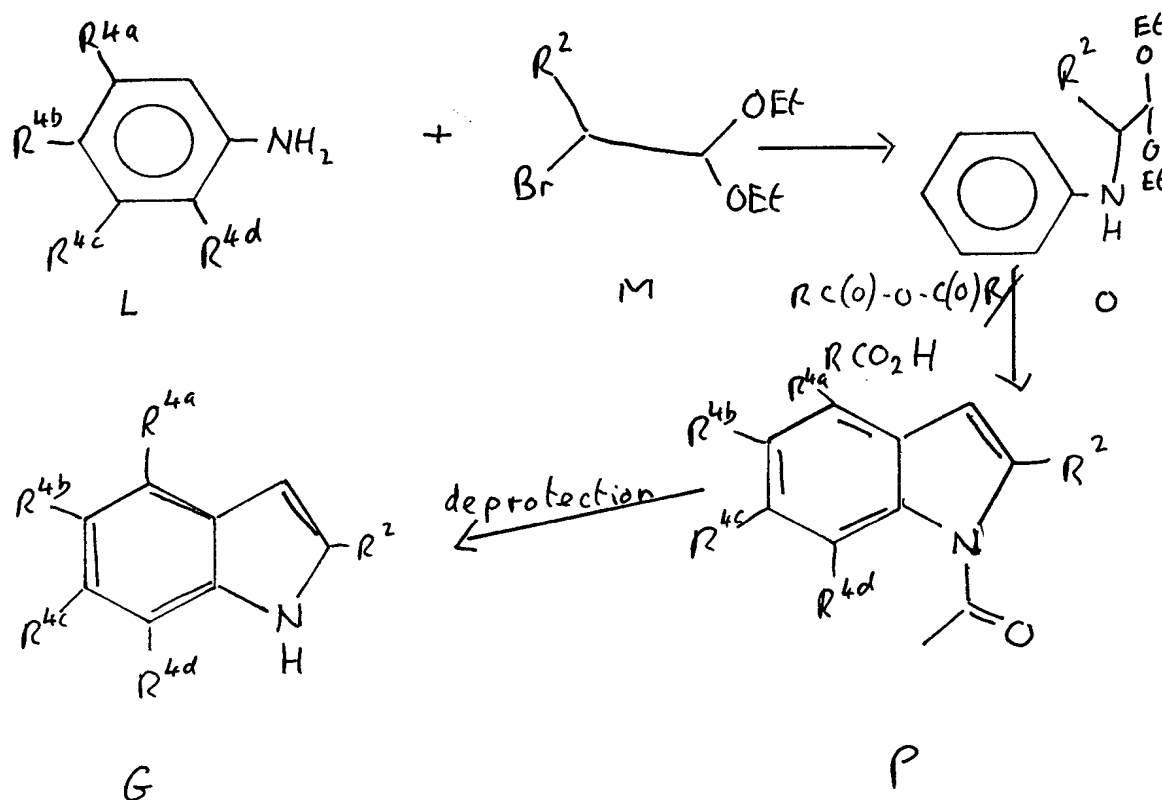


Reagents of Formula A, wherein  $R^1$  is a protecting group and  $R^2$  and  $R^{4a-d}$  are as defined in Formula I, are available by treating reagents of Formula A, wherein  $R^1$  is H and  $R^2$  and  $R^{4a-d}$  are as defined in Formula I, under standard conditions to introduce a protecting group on the pyrrolidine nitrogen. For example, reaction of indole A, wherein  $R^1$  is H, in the presence of di-  
 5 butyldicarbonate and a base, such as sodium hydroxide, would provide compounds of Formula A wherein  $R^1$  is the t-BOC protecting group.

10 The indoles of Formula G are either commercially available or can be prepared using standard procedures. For example, compounds of Formula G may

be prepared as shown in Scheme 3. 4-Substituted anilines of Formula L, wherein  $R^{4a-d}$  are as defined in Formula I, can be treated with reagents of Formula M, wherein  $R^2$  is as defined in Formula I, in the presence of a base such as sodium bicarbonate or potassium carbonate in an alcoholic solvent at temperatures in the range of 60-100 °C, to provide intermediates of Formula N. Preferred conditions are sodium bicarbonate in ethanol at around 80 °C. Intermediates of Formula N can be cyclized in the presence of reagents of Formula O, wherein R is, for example, methyl or trifluoromethyl (which is preferred) at temperatures in the range of 60-100 °C, to provide indoles of Formula P. The preferred conditions are trifluoroacetic anhydride and trifluoroacetic acid at refluxing temperatures. Finally, compounds of Formula P can be treated under standard deprotection conditions, for example alkali hydroxides in an alcoholic solvent, to provide indoles of Formula G, wherein  $R^2$  and  $R^{4a-d}$  are as defined in Formula I. Preferred conditions for this reaction are potassium hydroxide in ethanol at room temperature. The reagents of Formula L and M, are either commercially available or can be prepared using processes analogous to those established in the art.

Scheme 3



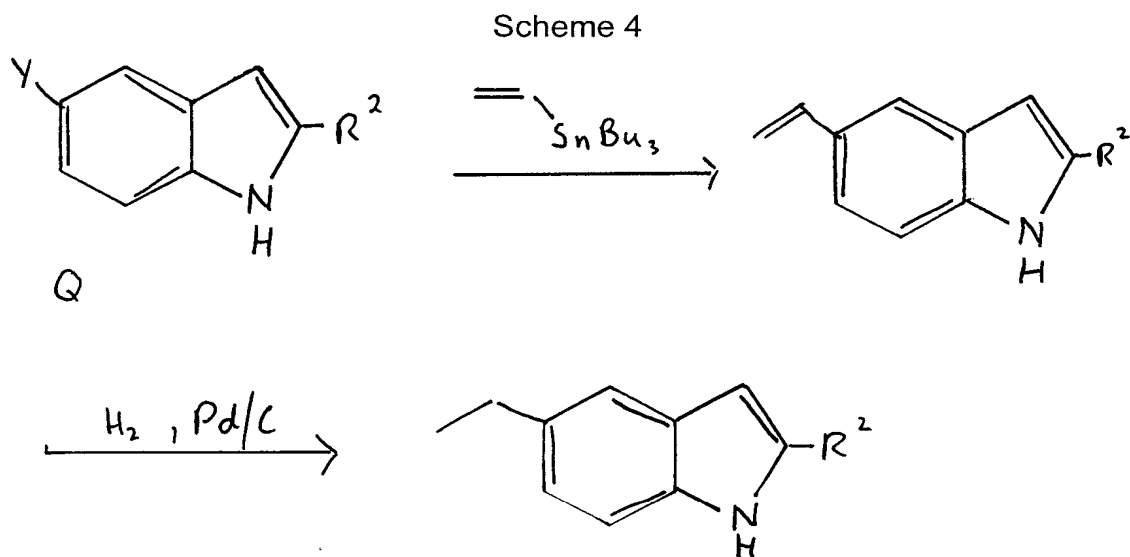
An alternative procedure for preparing indoles of Formula G wherein  $\text{R}^{4b}$  is vinyl or ethyl is shown in Scheme 4. Indoles of Formula Q, wherein Y is a suitable leaving group such as halo or triflate (preferably bromo) and  $\text{R}^2$  is as defined in

5 Indoles of Formula I, can be coupled with a vinyl trialkylstannane of, for example, Formula S, under standard palladium-cross coupling conditions to provide indoles of Formula G, wherein  $\text{R}^{4c}$  is vinyl and  $\text{R}^2$  is as defined in Formula I. It will be appreciated that other metal coupling reagents could be used in place of the vinyl stannane, for

10 example, a vinyl boronic acid, chloro zinc and the like. Preferred coupling

conditions include heating the indole and vinyl metal reagent in an inert solvent such as dimethylformamide or toluene in the presence of tetrakis(triphenylphosphine)palladium (0) at refluxing temperatures. Following the coupling reaction, the double bond of the vinyl group can be hydrogenated using catalytic amounts of palladium on carbon in an inert solvent (preferably ethyl acetate) in a hydrogen atmosphere at room temperature to provide indoles of Formula G wherein  $R^{4c}$  is ethyl. This procedure could also be used to prepare compounds of Formula G wherein  $R^{4a}$ ,  $R^{4c}$  or  $R^{4d}$  are ethyl by reacting the appropriately substituted indole Q as described above.

10



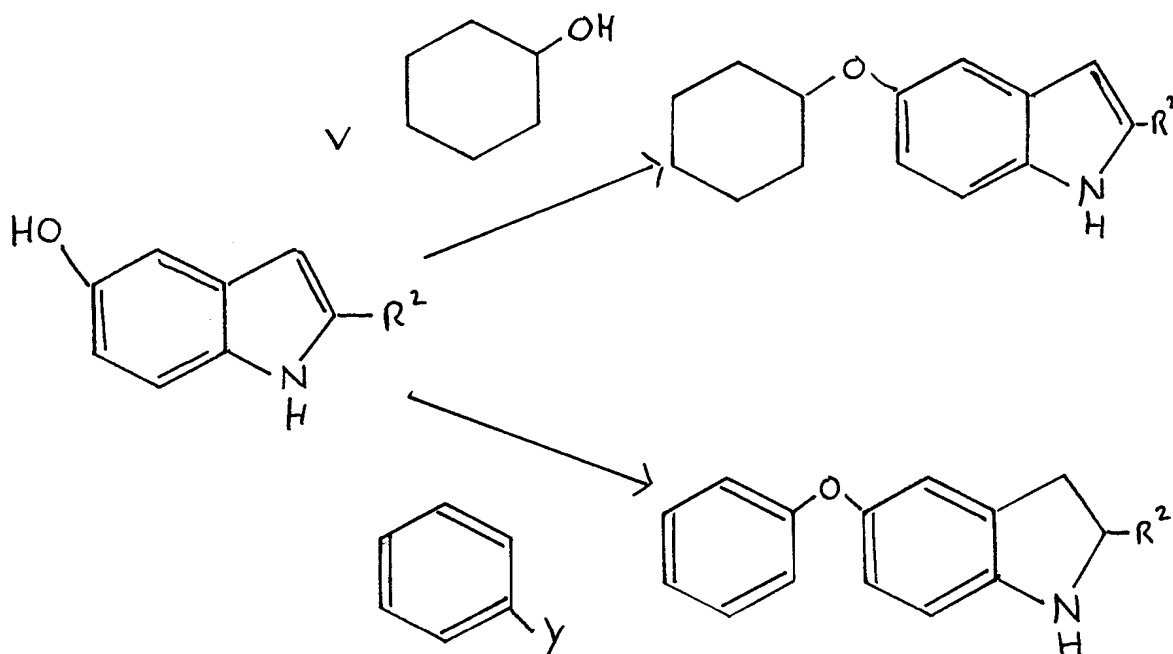
15

Indoles of Formula G, wherein  $R^{4b}$  is cyclooxy or phenoxy and  $R^2$  is as defined in Formula I, are also available from the corresponding 5-hydroxyindole T as shown in Scheme 5. Reaction of indole T with, for example, cyclohexanol U under standard Mitsunobu conditions (Mitsunobu, O. *Synthesis*, 1981:1-28) provides reagents of Formula G, wherein  $R^{4b}$  is cyclohexyloxy and  $R^2$  is as defined as Formula I. Reaction of indole T with reagent of Formula V wherein Y is an

20

appropriate leaving group such as halo, preferably iodo, under standard Ullman conditions (Fanta, F. E., *Chem. Rev.*, **64**, 1964:613) provides indoles of Formula G, wherein  $R^{4b}$  is phenoxy and  $R^2$  is as defined in Formula I. Preferred conditions are iodobenzene in the presence of potassium carbonate, copper (I) bromide and copper powder in N-methylpyrrolidine at 170 °C.

Scheme 5



10

The reactions shown in Schemes 4 and 5 could also be applied to indoles with the 3-(1- $R^1$ -2-pyrrolidinylmethyl) group in place. In some cases, the chemistries outlined above may have to be modified, for instance by use of protecting groups, to prevent side reactions due to reactive groups, such as reactive groups attached as substituents.

15

In another embodiment of the invention, the present compounds can be used

to distinguish 5-HT<sub>6</sub> receptors from other receptor subtypes, for example glutamate or opioid receptors, within a population of receptors, and in particular to distinguish between the 5-HT<sub>6</sub> and other 5-HT receptor subtypes. The latter can be achieved by incubating preparations of the 5-HT<sub>6</sub> receptor and one of the other 5-HT receptor subtypes (for example 5-HT<sub>2A</sub>) with a 5-HT<sub>6</sub>-selective compound of the invention and then incubating the resulting preparation with a radiolabeled serotonin receptor ligand, for example [<sup>3</sup>H]-serotonin. The 5-HT<sub>6</sub> receptors are then distinguished by determining the difference in membrane-bound activity, with the 5-HT<sub>6</sub> receptor exhibiting lesser radioactivity, i.e., lesser [<sup>3</sup>H]-serotonin binding, than the other 5-HT receptor subtype.

In another embodiment of the invention, the compound is provided in labeled form, such as radiolabeled form, e. g. labeled by incorporation within its structure <sup>3</sup>H or <sup>14</sup>C or by conjugation to <sup>125</sup>I. In another aspect of the invention, the compounds in labeled form can be used to identify 5-HT<sub>6</sub> receptor ligands by techniques common in the art. This can be achieved by incubating the receptor or tissue in the presence of a ligand candidate and then incubating the resulting preparation with an equimolar amount of radiolabeled compound of the invention such as [<sup>3</sup>H]-5-chloro-1-(4-fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole. 5-HT<sub>6</sub> receptor ligands are thus revealed as those that are not significantly displaced by the radiolabeled compound of the present invention. Alternatively, 5-HT<sub>6</sub> receptor ligand candidates may be identified by first incubating a radiolabeled form of a compound of the invention then incubating the resulting preparation in the presence of the candidate ligand. A more potent 5-HT<sub>6</sub> receptor ligand will, at equimolar concentration, displace the radiolabeled compound of the invention.

The present compounds are useful as pharmaceuticals for the treatment of various conditions in which the use of a 5-HT<sub>6</sub> antagonist is indicated, such as psychosis, schizophrenia, manic depression, depression, neurological disturbances, memory disturbances, Parkinsonism, amyotrophic lateral sclerosis,

Alzheimer's disease and Huntington's disease. In another of its aspects, the present invention provides pharmaceutical compositions useful to treat 5-HT<sub>6</sub>-related medical conditions, in which a compound of Formula I is present in an amount effective to antagonize 5-HT<sub>6</sub> receptor stimulation, together with a pharmaceutically acceptable carrier. In a related aspect, the invention provides a method for treating medical conditions for which a 5-HT<sub>6</sub> receptor antagonist is indicated, which comprises the step of administering to the patient an amount of a compound of Formula I effective to antagonize 5-HT<sub>6</sub> receptor stimulation, an a pharmaceutically acceptable carrier therefor.

10

For use in medicine, the compounds of the present invention can be administered in a standard pharmaceutical composition. The present invention therefore provides, in a further aspect, pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a Formula I compound or a pharmaceutically acceptable salt, solvate or hydrate thereof, in an amount effective to treat the target indication.

15

The compounds of the present invention may be administered by any convenient route, for example by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump or transdermal administration and the pharmaceutical compositions formulated accordingly.

20

Compounds of Formula I and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, or as solid forms such as tablets, capsules and lozenges. A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable pharmaceutical liquid carrier for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent. A composition in the form of a tablet can be prepared using any

25

30

suitable pharmaceutical carrier routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose. A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can  
5 be prepared using standard carriers and then filled into hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier, for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension filled into a soft gelatin capsule.

10 Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilized and then reconstituted with a suitable solvent just prior to administration.

15 Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose  
20 quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively, the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant  
25 which can be a compressed gas such as compressed air or an organic propellant such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer.

30 Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, wherein the active ingredient is formulated with a carrier such as sugar, acacia, tragacanth, or gelatin and glycerine. Compositions for rectal



administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Preferably, the composition is in unit dose form such as a tablet, capsule or ampoule. Suitable unit dosages, i.e. therapeutically effective amounts, can be determined during clinical trials designed appropriately for each of the conditions for which administration of a chosen compound is indicated and will of course vary depending on the desired clinical endpoint. Each dosage unit for oral administration may contain from 0.01 to 500 mg/kg (and for parenteral administration may contain from 0.1 to 50 mg) of a compound of Formula I, or a pharmaceutically acceptable salt thereof calculated as the free base, and will be administered in a frequency appropriate for initial and maintenance treatments. For laboratory use, the present compounds can be stored in packaged form for reconstitution and use.

## Experimental Examples

### Example 1: 5-Cyclohexyloxy-1H-indole:

Triphenylphosphine (10.3 g, 39.4 mmol) and 5-hydroxyindole (5 g, 36.9 mmol) were added to a solution of cyclohexanol (3.7 mL, 35.7 mmol) in THF (200 mL) at 0 °C. DEAD (5.9 mL, 39.4 mmol) was slowly added and the resulting solution was stirred for 1 week at room temperature. The solvent was removed *in vacuo* and flash chromatography (silica gel, 10% ethyl acetate in hexane) yielded 5-cyclohexyloxyindole (3.2 g, 40%).

### Example 2(a): (R)-3-[(N-Benzyloxycarbonyl)pyrrolidin-2-yl]carbonyl]-5-bromo-1H-indole

To a stirred solution of N-benzyloxycarbonyl-R-proline (2.5 g, 10.0 mmol) in anhydrous methylene chloride was added a solution of oxalyl chloride (2M solution

in methylene chloride, 7 mL, 15.0 mmol). The resulting mixture was stirred at room temperature under argon for 2 hours. The solvent and excess oxalyl chloride were evaporated under reduced pressure and the crude product washed with hexane (3x 10 mL) and evaporated to dryness to provide N-benzyloxycarbonyl-R-proline acid chloride which was used directly for the next reaction.

N-Benzyloxycarbonyl-R-proline acid chloride from the above reaction was dissolved in anhydrous diethyl ether (30 mL) and added at 0 °C to a solution of 5-bromoindole (2.9 g, 15.0 mmol) and *t*-butylmagnesium chloride (2M solution in diethyl ether, 8.3 mL, 16.5 mmol) in anhydrous diethyl ether (30 mL). The resulting mixture was stirred at room temperature under argon for 45 minutes and then ethyl acetate (150 mL) and saturated sodium bicarbonate (30 mL) were added. The organic layer was dried and evaporated under reduced pressure to provide a yellow oil. The title compound was crystallized using hexane/ethyl acetate (9:1) to provide a white solid (3.07 g, 72%). mp 95-96 °C.

In a like manner, the following additional compounds were prepared:

(b) (R)-3-[(N-Benzyloxycarbonylpyrrolidin-2-yl)carbonyl]-5-methyl-1H-indole: from 5-methyl-1H-indole;

(c) (R)-3-[(N-Benzyloxycarbonylpyrrolidin-2-yl)carbonyl]-5-chloro-1H-indole: from 5-chloro-1H-indole;

(d) (R)-3-[(N-Benzyloxycarbonylpyrrolidin-2-yl)carbonyl]-5-fluoro-1H-indole: from 5-fluoro-1H-indole;

(e) (R)-3-[(N-Benzyloxycarbonylpyrrolidin-2-yl)carbonyl]-1H-indole: from 1H-indole;

(f) (R)-3-[(N-Benzyloxycarbonylpyrrolidin-2-yl)carbonyl]-5-benzyloxy-1H-indole: from 5-benzyloxy-1H-indole; and

(g) (R)-3-[(N-Benzyloxycarbonylpyrrolidin-2-yl)carbonyl]-5-cyclohexyloxy-1H-indole: from 5-cyclohexyloxy-1H-indole (Example 1).

Example 3(a): (R)-5-Methyl-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole

A solution of LAH (39 mL, 1M in THF, 39 mmol) was added slowly to a cooled (0 °C) solution of (R)-3-[(N-benzyloxycarbonylpyrrolidin-2-yl)carbonyl]-5-methyl-1H-indole (Example 1b, 9.5 mmol) in THF (100 mL). Once the addition was completed, the reaction mixture was stirred at reflux overnight prior to quenching with sodium sulfate decahydrate. The product was taken into ethyl acetate, filtered to remove the solid residue, and the solvent was removed *in vacuo*. The product was taken into ethyl acetate, filtered to remove the solid residue, and the solvent was removed *in vacuo*. Flash chromatography (silica gel, 6% 2M methanolic ammonia in dichloromethane) yielded (R)-5-methyl-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (52%; yellow oil; HRMS-FAB<sup>+</sup> for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>: calculated MH<sup>+</sup>:229.1705; found MH<sup>+</sup>:229.1706).

In a like manner, the following additional compounds were prepared:

- (b) (R)-5-Bromo-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole: from (R)-3-[(N-benzyloxycarbonylpyrrolidin-2-yl)carbonyl]-5-bromo-1H-indole (Example 2a);  
(c) (R)-5-Chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole: from (R)-3-[(N-benzyloxycarbonylpyrrolidin-2-yl)carbonyl]-5-chloro-1H-indole (Example 2c);  
(d) (R)-5-Fluoro-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole: from (R)-3-[(N-benzyloxycarbonylpyrrolidin-2-yl)carbonyl]-5-fluoro-1H-indole (Example 2b);  
(e) (R)-3-(1-Methyl-2-pyrrolidinylmethyl)-1H-indole: from (R)-3-[(N-benzyloxycarbonylpyrrolidin-2-yl)carbonyl]-1H-indole (Example 2e);  
(f) (R)-5-Benzyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole: from (R)-3-[(N-benzyloxycarbonylpyrrolidin-2-yl)carbonyl]-5-benzyloxy-1H-indole (Example 2f);  
and  
(g) (R)-5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole: from (R)-3-[(N-benzyloxycarbonylpyrrolidin-2-yl)carbonyl]-5-cyclohexyloxy-1H-indole (Example 2g).

Example 4: (R)-5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole

n-Butyllithium (0.19 mL, 1.45M in hexane, 0.28 mmol) was added to a solution of  
5 (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3g, 77.1  
mg, 0.25 mmol) in THF (1 mL) at -78 °C; the temperature was raised to 0 °C and  
the mixture was stirred for 40 min. After recooling to -78 °C, phenylsulfonyl  
chloride (60 µL, 0.47 mmol) was added and the mixture was allowed to warm to  
room temperature slowly (overnight). The mixture was quenched with water (5 mL)  
10 and extracted into dichloromethane. The organic layer was washed sequentially  
with water and brine, and dried over sodium sulfate. Purification by flash  
chromatography (silica gel, 1-4% 2M methanolic ammonia in chloroform) yielded  
(R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole (19.1  
mg, 17%, HRMS-FAB<sup>+</sup> for C<sub>26</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>S: calculated MH<sup>+</sup>:453.22119; found  
15 MH<sup>+</sup>:453.22550).

Example 5(a): (R)-3-(1-Methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole

Sodium bis(trimethylsilyl)amide (0.25 mL, 1M in THF, 0.25 mmol) was added to a  
20 solution of (R)-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3e, 25.8 mg,  
0.12 mmol) in THF (1.5 mL) at -78 °C and the mixture was stirred for 1 h.  
Phenylsulfonyl chloride (50 µL, 0.39 mmol) was added and the mixture stirred at  
room temperature for 1h. prior to quenching with water (6 drops) and silica gel  
(~1g). Purification using solid phase extraction tubes (1000 mg silica) eluting with  
25 2M methanolic ammonia in dichloromethane (0-4%) yielded (R)-3-(1-methyl-2-  
pyrrolidinylmethyl)-1-phenylsulfonylindole (19.7 mg, 46%, HRMS-FAB<sup>+</sup> for  
C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>S: calculated MH<sup>+</sup>:355.14801; found MH<sup>+</sup>:355.14837).

In a like manner, the following additional compounds were prepared:

- (b) (R)-1-(4-Methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (28.1 mg, 61%); from (R)-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3e, 25.8 mg, 0.12 mmol) and 4-methoxyphenylsulfonyl chloride (50 mg, 0.24 mmol); HRMS-FAB<sup>+</sup> for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>S: calculated MH<sup>+</sup>:385.15860; found MH<sup>+</sup>:385.15891.
- (c) (R)-1-(4-Fluorophenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (27.2 mg, 61%); from (R)-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3e, 25.8 mg, 0.12 mmol) and 4-fluorophenylsulfonyl chloride (50 mg, 0.26 mmol); HRMS-FAB<sup>+</sup> for C<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>SF: calculated MH<sup>+</sup>:373.13861; found MH<sup>+</sup>:373.13872.
- (d) (R)-5-Chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole: (18.1 mg, 46% yield); from (R)-5-chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3c, 25.8 mg, 0.103 mmol) and phenylsulfonyl chloride (36.3 mg, 0.206 mmol), HRMS-FAB<sup>+</sup>: C<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>SCl, calculated MH<sup>+</sup>: 389.10904; found MH<sup>+</sup>: 389.10749.
- (e) (R)-5-Chloro-1-(4-methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (16.5 mg, 40% yield); from (R)-5-chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3c, 25.9 mg, 0.103 mmol) and 4-methoxyphenylsulfonyl chloride (42.4 mg, 0.206 mmol), HRMS-FAB<sup>+</sup>: C<sub>21</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub>SCl, calculated MH<sup>+</sup>: 419.11963; found MH<sup>+</sup>: 419.11552.
- (f) (R)-5-Chloro-1-(4-fluorophenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (21.1 mg, 52% yield); from (R)-5-chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3c, 26.8 mg, 0.107 mmol) and 4-fluorophenylsulfonyl chloride (41.5 mg, 0.214 mmol), HRMS-FAB<sup>+</sup>: C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>SClF, calculated MH<sup>+</sup>: 407.09964; found MH<sup>+</sup>: 407.10291.
- (g) (R)-1-Benzoyl-3-(1-methyl-2-pyrrolidinylmethyl)indole: (21.4 mg, 56%); from

(R)-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3e, 26.0 mg, 0.12 mmol) and benzoyl chloride (50  $\mu$ L, 0.43 mmol); HRMS-FAB<sup>+</sup> for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O: calculated MH<sup>+</sup>:319.18103; found MH<sup>+</sup>:319.17955.

- 5 (h) (R)-1-(4-Methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (30 mg, 72%); from (R)-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3e, 26 mg, 0.12 mmol) and 4-methoxybenzoyl chloride (50  $\mu$ L, 0.34 mmol); HRMS-FAB<sup>+</sup> for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: calculated MH<sup>+</sup>:349.19159; found MH<sup>+</sup>:349.19034.
- 10 (i) (R)-1-(4-Fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (34.8 mg, 86%); from (R)-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3e, 25.9 mg, 0.12 mmol) and 4-fluorobenzoyl chloride (50  $\mu$ L, 0.42 mmol); HRMS-FAB<sup>+</sup> for C<sub>21</sub>H<sub>21</sub>N<sub>2</sub>OF: calculated MH<sup>+</sup>:337.17163; found MH<sup>+</sup>:337.17138.
- 15 (j) (R)-1-(2-Chlorobenzoyl)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)indole: (18.6 mg, 56%); from (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3g, 22.8 mg, 0.073 mmol) and 2-chlorobenzoyl chloride (19.5  $\mu$ L, 0.15 mmol); HRMS-FAB<sup>+</sup> for C<sub>27</sub>H<sub>31</sub>N<sub>2</sub>O<sub>2</sub>Cl: calculated MH<sup>+</sup>:451.21524; found MH<sup>+</sup>:451.21488.
- 20 (k) (R)-5-Cyclohexyloxy-1-(2-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (15.4 mg, 44%); from (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3g, 24.6 mg, 0.079 mmol) and 2-methoxybenzoyl chloride (24  $\mu$ L, 0.16 mmol); HRMS-FAB<sup>+</sup> for C<sub>28</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub>:  
25 calculated MH<sup>+</sup>:447.26477; found MH<sup>+</sup>:447.26434.
- (l) (R)-5-Cyclohexyloxy-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (24.3 mg, 69%); from (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3g, 24.7 mg, 0.079 mmol) and  
30 4-methoxybenzoyl chloride (24  $\mu$ L, 0.16 mmol); HRMS-FAB<sup>+</sup> for C<sub>28</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub>:

calculated  $MH^+$ :447.26477; found  $MH^+$ :447.26630.

(m) (R)-5-Cyclohexyloxy-1-(3,4-methylenedioxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (24.8 mg, 68%); from (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3g, 24.7 mg, 0.079 mmol) and 3,4-methylenedioxybenzoyl chloride (31 mg, 0.17 mmol); HRMS-FAB<sup>+</sup> for  $C_{28}H_{32}N_2O_4$ : calculated  $MH^+$ :461.24402; found  $MH^+$ :461.24525.

(n) (R)-5-Cyclohexyloxy-1-(2,6-dichlorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (28.7 mg, 75%); from (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3g, 24.7 mg, 0.079 mmol) and 2,6-dichlorobenzoyl chloride (23  $\mu$ L, 0.16 mmol).

(o) (R)-5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(2-thienoyl)indole: (15.4 mg, 46%); from (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3g, 24.8 mg, 0.079 mmol) and 2-thiophenecarbonyl chloride (17  $\mu$ L, 0.16 mmol); HRMS-FAB<sup>+</sup> for  $C_{25}H_{30}N_2O_2S$ : calculated  $MH^+$ :423.21063; found  $MH^+$ :423.20947.

(p) (R)-1-Benzoyl-5-chloro-3-(1-methyl-2-pyrrolidinylmethyl)indole: (28 mg, 66% yield); from (R)-5-chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3c, 30 mg, 0.12 mmol) and benzoyl chloride (33.7 mg, 0.24 mmol), HRMS-FAB<sup>+</sup>:  $C_{21}H_{21}N_2OCl$ , calculated  $MH^+$ : 353.14206; found  $MH^+$ : 353.14528.

(q) (R)-5-Chloro-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (24 mg, 52% yield); from (R)-5-chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3c, 30 mg, 0.12 mmol) and 4-methoxybenzoyl chloride (40.9 mg, 0.24 mmol), HRMS-FAB<sup>+</sup>:  $C_{22}H_{23}ClN_2O_2$ , calculated  $MH^+$ : 383.15262; found  $MH^+$ : 383.14917.

(r) (R)-5-Chloro-1-(4-fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (6.8 mg, 15% yield); from (R)-5-chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3c, 30 mg, 0.12 mmol) and 4-fluorobenzoyl chloride (38.1 mg, 0.24 mmol), HRMS-FAB<sup>+</sup>: C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>OCIF, calculated MH<sup>+</sup>: 371.13263; found MH<sup>+</sup>: 371.13285.

Example 6(a): (R)-5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-methylxanthyl)indole

Sodium bis(trimethylsilyl)amide (0.49 mL, 1M in THF, 0.49 mmol) was added to a solution of (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3g, 76.3 mg, 0.24 mmol) in THF (2.5 mL) at -78 °C and the mixture was stirred for 1 h. Carbon disulfide (30 µL, 0.50 mmol) was added and the mixture stirred at room temperature for 1h. at -78 °C prior to quenching with methyl iodide (30 µL, 0.48 mmol). The mixture was allowed to warm to room temperature slowly (overnight). Purification by flash chromatography (silica gel, 2M methanolic ammonia in dichloromethane (2-4%) yielded (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-methylxanthyl)indole (42.7 mg, 43%, HRMS-FAB<sup>+</sup> for C<sub>22</sub>H<sub>30</sub>N<sub>2</sub>OS<sub>2</sub>: calculated MH<sup>+</sup>:403.18777; found MH<sup>+</sup>:403.18795).

In a like manner, the following additional compounds were prepared:

(b) (R)-5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-[S-(4-cyanobenzyl)xanthyl]indole: (14.5 mg, 18%); from (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3g, 50 mg, 0.16 mmol), carbon disulfide (25 µL, 0.41 mmol) and 4-cyanobenzyl bromide (64 mg, 0.33 mmol); HRMS-FAB<sup>+</sup> for C<sub>29</sub>H<sub>33</sub>N<sub>3</sub>OS<sub>2</sub>: calculated MH<sup>+</sup>:504.21432; found MH<sup>+</sup>:504.21887.

(c) (R)-5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-



benzylxanthyl)indole: (10.7 mg, 13%); from (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3g, 51.9 mg, 0.17 mmol), carbon disulfide (25  $\mu$ L, 0.41 mmol) and benzyl bromide (56  $\mu$ L, 0.47 mmol); HRMS-FAB<sup>+</sup> for C<sub>28</sub>H<sub>34</sub>N<sub>2</sub>OS<sub>2</sub>: calculated MH<sup>+</sup>:479.21909; found MH<sup>+</sup>:479.21784.

5

(d) (R)-5-Methyl-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-methylxanthyl)indole: (21.0 mg, 36%); from (R)-5-methyl-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3a, 41.3 mg, 0.181 mmol), carbon disulfide (28 mg, 0.362 mmol) and methyl iodide (0.362 mmol); HRMS-FAB<sup>+</sup> for C<sub>17</sub>H<sub>23</sub>N<sub>2</sub>S<sub>2</sub> calculated MH<sup>+</sup>:

10 319.13028; found MH<sup>+</sup>: 319.13390.

(e) (R)-5-Fluoro-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-methylxanthyl)indole: (.055 g, 66%) from (R)-5-fluoro-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3d, 0.060 g, .258 mmol) and carbon disulfide ( 39 Mg, 0.516 mmol) and methyl iodide ( 73 Mg, 0.516 mmol); HRMS-FAB<sup>+</sup> for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>S<sub>2</sub>F calculated MH<sup>+</sup>: 323.10519; found MH<sup>+</sup>: 323.10585.

15

(f) (R)-1-(S-Benzylxanthyl)-5-fluoro-(1-methyl-2-pyrrolidinylmethyl)indole: (19.3 mg, 53%) from (R)-5-fluoro-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3d, 20.9 mg, 0.092 mmol) and carbon disulfide (14.1 mg, 0.184 mmol) and benzyl bromide (31.4 mg, 0.184 mmol); HRMS- FAB<sup>+</sup> for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>S<sub>2</sub>F calculated MH<sup>+</sup>: 399.13651; found MH<sup>+</sup>: 399.13687.

20

(g) (R)-1-(S-Allylxanthyl)-5-fluoro-3-(1-methyl-2-pyrrolidinylmethyl)indole: (22.8 mg, 65%) from (R)-5-fluoro-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3d, 23.0 mg, 0.101 mmol), carbon disulfide (15.3 mg, 0.202 mmol) and allyl bromide (24.5 mg, .202 mmol); HRMS-FAB<sup>+</sup> for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>S<sub>2</sub>F calculated MH<sup>+</sup>: 349.12085; found MH<sup>+</sup>: 349.12188.

25

30 (h) (R)-5-Fluoro-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-propargylxanthyl)indole:

(19.0 mg, 50%) from (R)-5-fluoro-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3d, 24.9 mg, 0.109 mmol), carbon disulfide (16.6 mg, 0.218 mmol) and propargyl bromide (25.9 mg, 0.218 mmol); HRMS-FAB<sup>+</sup> for C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>S<sub>2</sub>F calculated MH<sup>+</sup>: 347.10519; found MH<sup>+</sup>: 347.10180.

5

(i) (R)-3-(1-Methyl-2-pyrrolidinylmethyl)-1-(S-methylxanthyl)indole: (32 mg, 39%) from (R)-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3e, 58 mg, 0.273 mmol), carbon disulfide (41 mg, 0.546 mmol) and methyl iodide (77 mg, 0.546 mmol); HRMS-FAB<sup>+</sup> for C<sub>16</sub>H<sub>21</sub>N<sub>2</sub>S<sub>2</sub> calculated MH<sup>+</sup>: 305.11462, found  
10 MH<sup>+</sup>: 305.11289.

(j) (R)-1-(S-Benzylxanthyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (17.3 mg, 36%) from (R)-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3e, 27.0 mg, 0.126 mmol), carbon disulfide (19.1 mg, 0.252 mmol) and benzyl bromide  
15 (43.1 mg, 0.252 mmol); HRMS-FAB<sup>+</sup> for C<sub>22</sub>H<sub>25</sub>N<sub>2</sub>S<sub>2</sub> calculated MH<sup>+</sup>: 381.14590; found MH<sup>+</sup>: 381.14467.

(k) (R)-1-(S-Allylxanthyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole: (19.2 mg, 50%) from (R)-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3e, 24.9  
20 mg, 0.116 mmol) and carbon disulfide (17.7 mg, 0.232 mmol) and allyl bromide (28.0 mg, 0.232 mmol); HRMS-FAB<sup>+</sup> for C<sub>18</sub>H<sub>23</sub>N<sub>2</sub>S<sub>2</sub> calculated MH<sup>+</sup>: 331.13028; found MH<sup>+</sup>: 331.13324.

Example 7(a): (R)-5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-benzoylindole  
25

Benzoyl chloride (0.10 mL, 0.86 mmol) was added to a solution of (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3g, ~75 mg, 0.24 mmol), triethylamine (0.20 mL, 1.4 mmol) and DMAP (23 mg, 0.19 mmol) in  
30 dichloromethane (2.5 mL). The mixture was stirred for 15 h. prior to quenching with water (25 mL) and extraction into dichloromethane. The organic layer was

washed with brine and dried over sodium sulfate. Purification by flash chromatography (silica gel, 2M methanolic ammonia in chloroform (1.5-3.3%) yielded (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-benzoylindole (20.1 mg, 20%, HRMS-FAB<sup>+</sup> for C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>: calculated MH<sup>+</sup>:417.25421; found MH<sup>+</sup>:417.25475).

In a like manner, the following additional compounds were prepared:

(b) (R)-5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(4-methylphenylsulfonyl)indole: (9.2 mg, 11%); from (R)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3g, 54.2 mg, 0.17 mmol) and 4-methylphenylsulfonyl chloride (41.2 mg, 0.22 mmol); HRMS-FAB<sup>+</sup> for C<sub>27</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub>S: calculated MH<sup>+</sup>:467.23685; found MH<sup>+</sup>:467.24074;

(c) (R)-5-Fluoro-1-(4-methylphenylsulphonyl)-3-(1-methyl-2-pyrrolidinylmethyl)-indole: (11.5 mg, 17%) from (R)-5-fluoro-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3d, 40.2 mg, 0.17 mmol) and 4-methylphenylsulphonyl chloride (36.2 mg, 0.19 mmol); HRMS-FAB<sup>+</sup> for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>SF calculated MH<sup>+</sup>: 387.15427; found MH<sup>+</sup>: 387.15548;

(d) (R)-1-Benzoyl-5-bromo-3-(1-methyl-2-pyrrolidinylmethyl) indole: (198 mg, 50%) from (R)-5-bromo-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3b, 90 mg, 0.99 mmol) and benzoyl chloride (0.15 g, 1.09 mmol); HRMS-FAB<sup>+</sup> for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>OBr calculated MH<sup>+</sup>: 397.09155; found MH<sup>+</sup>: 397.09155.

e) (R)-5-Benzyloxyindole-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole: from 5-benzyloxyindole-3-(1-methyl-2-pyrrolidinylmethyl)indole (Example 3f, 200 mg, 0.62 mmol) and phenylsulfonyl chloride (95.5 uL, 0.75 mmol).

Example 8: (R)-5-Benzyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(N-

methylcarboxamido)indole

N-Methyl isocyanate (18.7  $\mu$ L, 0.32 mmol) was added to a solution of (R)-5-benzyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1H-indole (Example 3f, 75 mg, 0.23 mmol) and triethylamine (0.17 mL, 1.2 mmol) in toluene (3 mL) and the mixture was stirred at reflux until disappearance of the starting indole was indicated by tlc. The cooled reaction mixture was diluted with dichloromethane and washed sequentially with water and brine. Flash chromatography (silica gel, 7% 2M methanolic ammonia in dichloromethane) yielded (R)-5-benzyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(N-methylcarboxamido)indole (48.2 mg, 54%).

Example 9: (R)-5-Hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(N-methylcarboxamido)indole

Palladium on carbon (10%, 20 mg) was added to a solution of (R)-5-benzyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(N-methylcarboxamido)-1H-indole (Example 8, 40 mg, 0.105 mmol) in ethyl acetate (1 mL) and methanol (1 mL) and the mixture was stirred under an atmosphere of hydrogen until disappearance of the starting indole was indicated by tlc. Removal of the catalyst by filtration followed by flash chromatography (silica gel, 10% 2M methanolic ammonia in dichloromethane) yielded (R)-5-hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(N-methylcarboxamido)indole.

Example 10: (R)-1-Phenylsulfonyl-5-hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)indole

A solution of (R)-5-benzyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole (Example 7e, 2.01 g, 4.36 mmol) and 10% Pd/C (0.64 g, 0.436 mmol) in ethanol (25 mL) was stirred under an atmosphere of H<sub>2</sub>. Filtration to remove the catalyst followed by flash chromatography (silica gel) yielded (R)-5-

hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole (1.5 g, 93%; HRMS-FAB<sup>+</sup>: C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>S, calculated MH<sup>+</sup>: 371.14294; found MH<sup>+</sup>: 371.14081).

Example 11: (R)-1-Phenylsulfonyl-5-phenoxy-3-(1-methyl-2-pyrrolidinylmethyl)indole

A solution of (R)-5-hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole (Example 10, 74 mg, 0.20 mmol) and iodobenzene (61.2 mg, 0.3 mmol) with K<sub>2</sub>CO<sub>3</sub> (41.4 mg 0.30 mmol), CuBr (17.2 0.12 mmol) and Cu powder (10 mg, 0.15 mmol) in NMP (0.7 mL) was heated at 170 °C. Aqueous workup and flash chromatography (silica gel) yielded (R)-3-(1-methyl-2-pyrrolidinylmethyl)5-phenoxy-1-phenylsulfonylindole (5.8 mg, 8%, HRMS-FAB<sup>+</sup>: C<sub>26</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S, calculated MH<sup>+</sup>: 447.17422; found MH<sup>+</sup>: 447.17240).

Example 12(a): (R)-2-Benzyl-5-hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole

n-Butyllithium (0.10 mL, 1.45M in hexane, 0.14 mmol) was added to a solution of (R)-5-benzyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole (Example 7e, 24 mg, 0.052 mmol) in THF (2 mL) at -78 °C; the temperature was raised to 0 °C and the mixture was stirred for 20 min. After recooling to -78 °C, benzyl bromide (18 µL, 0.15 mmol) was added and the mixture was stirred for 1h at 78 °C; then 15 min. without cooling prior to quenching with water and extraction with ethyl acetate. The organic layer was washed sequentially with water and brine, and dried over sodium sulfate. Palladium on carbon (10%) was added to a solution of the crude product in methanol (2 mL) and the mixture was stirred under an atmosphere of hydrogen for 1.5 h. Removal of the catalyst by filtration followed by flash chromatography (silica gel, 0-10% 2M methanolic ammonia in dichloromethane) yielded (R)-2-benzyl-5-hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole (12.5 mg, 40%; HRMS-FAB<sup>+</sup> for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S calculated

MH<sup>+</sup>:461.18988; found MH<sup>+</sup>:461.18724).

- (b) (R)-5-Hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole: isolated as a side product from the above reaction (8.0 mg, 50%; HRMS-FAB<sup>+</sup> for
- 5 C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>S: calculated MH<sup>+</sup>:371.14294; found MH<sup>+</sup>:371.14078).

**Summary of Exemplified Compounds**

	<b>R<sup>1</sup></b>	<b>R<sup>2</sup></b>	<b>R<sup>3</sup></b>	<b>R<sup>4b</sup> *</b>	<b>Example #</b>
	Me	H			4
5	Me	H		H	5a
	Me	H		H	5b
	Me	H		H	5c
	Me	H		Cl	5d
	Me	H		Cl	5e
10	Me	H		Cl	5f
	Me	H		H	5g
	Me	H		H	5h
	Me	H		H	5i
	Me	H			5j
15	Me	H			5k

	<b>R<sup>1</sup></b>	<b>R<sup>2</sup></b>	<b>R<sup>3</sup></b>	<b>R<sup>4b *</sup></b>	<b>Example #</b>
	Me	H			5l
	Me	H			5m
5	Me	H			5n
	Me	H			5o
	Me	H		Cl	5p
	Me	H		Cl	5q
	Me	H		Cl	5r
10	Me	H			6a
	Me	H			6b
	Me	H			6c
	Me	H		Me	6d
	Me	H		F	6e
15	<b>R<sup>1</sup></b>	<b>R<sup>2</sup></b>	<b>R<sup>3</sup></b>	<b>R<sup>4b *</sup></b>	<b>Example #</b>



	Me	H		F	6g
	Me	H		F	6h
	Me	H		H	6i
	Me	H		H	6j
5	Me	H		H	6k
	Me	H			7a
	Me	H			7b
	Me	H		F	7c
	Me	H		Br	7d
10	Me	H			7e
	Me	H			8
	Me	H		OH	9

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4b</sup> *	Example #
Me	H			11
Me	Bn		OH	12a
Me	H		OH	12b

\* R<sup>4a</sup>, R<sup>4c</sup> and R<sup>4d</sup> are all H.

#### Example 13: Binding Affinity for the 5-HT<sub>6</sub> Receptor

- 10 All of the compounds of the invention were evaluated using cell types receptive specifically to the 5-HT<sub>6</sub> receptor (for cloning and characterization of the human 5-HT<sub>6</sub> receptor see Kohen, *et al.* J. Neurochemistry, 66, 1996: 47-56). The assay protocol generally entailed the incubation of membranes prepared from cells expressing the 5-HT<sub>6</sub> receptor with <sup>3</sup>H-LSD. Increasing levels of the test
- 15 compound were incubated with the radioligand and the membrane homogenates prepared from the recombinant cells. After a 60 minute incubation at 37 °C, the incubation was terminated by vacuum filtration. The filters were washed with buffer and the filters were counted for radioactivity using liquid scintillation spectrometry. The affinity of the test compound for the 5-HT<sub>6</sub> receptor was determined by
- 20 computer-assisted analysis of the data and determining the amount of the compound necessary to inhibit 50% of the binding of the radioligand to the receptor. Concentrations ranging from 10<sup>-11</sup> M to 10<sup>-5</sup> M of the test compound were evaluated. For comparison, the affinity of clozapine for the 5-HT<sub>6</sub> receptor (K<sub>i</sub> ~ 3 nm) was used as a standard. All of the compounds of the invention exhibited
- 25 affinity for the human 5-HT<sub>6</sub> receptor, with K<sub>i</sub>'s of not greater than 200 nM. Preferred compounds, those of examples 4, 5a-d, 5g, 5i-l, 5o-r, 7a, 7d, 10 and 12b, exhibited K<sub>i</sub>'s of not greater than 10 nM. Still more preferred are compounds, those of examples 4, 5d, 5p, 7c, 7e, and 7d, which exhibited K<sub>i</sub>'s of not greater

than 1 nM. The compounds of the invention also bound to the human 5-HT<sub>6</sub> receptor in a selective manner, relative to the human 5-HT<sub>2C</sub> and 5-HT<sub>7</sub> receptors. That is, the compounds of the invention bound to the human 5-HT<sub>6</sub> receptor with at least a 2-fold greater affinity, relative to the human 5-HT<sub>2C</sub> and 5-HT<sub>7</sub> receptors.

5 The compounds of examples 5k, 5n, 5d, 5j and 5r bound to the human 5-HT<sub>6</sub> receptor with at least a 36-fold greater affinity, relative to the human 5-HT<sub>2C</sub> and 5-HT<sub>7</sub> receptors. The compounds of examples 5k, 5d and 5j bound to the human 5-HT<sub>6</sub> receptor with at least a 100-fold greater affinity, relative to the human 5-HT<sub>2C</sub> and 5-HT<sub>7</sub> receptors.

10

Example 14: Effect of Compounds on the cAMP Response of Human 5-HT<sub>6</sub> Receptors

The antagonist (or agonist ) property of compounds for human 5-HT<sub>6</sub> receptors was determined by testing their effect on cAMP accumulation in stably transfected HEK293 cells.

15 Binding of an agonist to the human 5-HT<sub>6</sub> receptor will lead to a increase in adenyl cyclase activity. A compound which is an agonist will show an increase in cAMP production and a compound which is an antagonist will block the agonist effect.

20 *Cell Assay:* Human 5-HT<sub>6</sub> receptors were cloned and stably expressed in HEK293 cells. These cells were plated in 6 well plates in DMEM/F12 media with 10% fetal calf serum (FCS) and 500 µg/mL G418 and incubated at 37°C in a CO<sub>2</sub> incubator.

25 The cells were allowed to grow to about 70% confluence before initiation of the experiment.

On the day of the experiment, the culture media was removed, and the cells were washed once with serum free medium (SFM). Two mL of SFM+IBMX media was added and incubated at 37°C for 10 min. The media were removed and fresh

30

SFM+IBMX media containing various compounds, and 1  $\mu$ M serotonin (as antagonist) were added to the appropriate wells and incubated for 30 min. Following incubation, the media were removed and the cells were washed once with 1 mL of PBS (phosphate buffered saline). Each well was treated with 1 mL  
5 cold 95% ethanol and 5 mM EDTA (2:1) at 4°C for 1 hour. The cells were then scraped and transferred into Eppendorf tubes. The tubes were centrifuged for 5 min at 4°C, and the supernatants were stored at 4 °C until assayed.

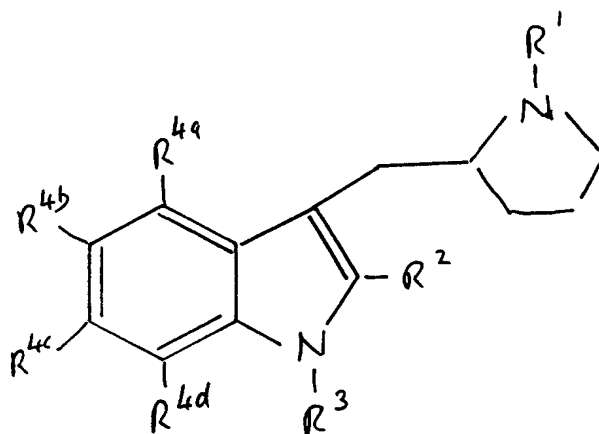
*cAMP Measurement:* cAMP content was determined by EIA (enzyme-immunoassay) using the Amersham Biotrak cAMP EIA kit (Amersham RPN 225).  
10 The procedure used is as described for the kit. Briefly, cAMP is determined by the competition between unlabeled cAMP and a fixed quantity of peroxidase-labelled cAMP for the binding sites on anti-cAMP antibody. The antibody is immobilized onto polystyrene microtitre wells precoated with a second antibody. The reaction  
15 is started by adding 50  $\mu$ L peroxidase-labeled cAMP to the sample (100  $\mu$ L) preincubated with the antiserum (100  $\mu$ L) for 2 hours at 4 °C. Following 1 hour incubation at 4 °C, the unbound ligand is separated by a simple washing procedure. Then an enzyme substrate, tetramethylbenzidine (TMB), is added and incubated at room temperature for 60 min. The reaction is stopped by the addition  
20 of 100  $\mu$ L 1.0 M sulphuric acid and the resultant color read by a microtitre plate spectrophotometer at 450 nM within 30 minutes.

All of the compounds of the invention which were tested in the above assays were found to be antagonists. The potency of compounds of the invention as  
25 antagonists is expressed as an  $EC_{50}$ , which is the concentration causing 50% inhibition of the serotonin-stimulated cAMP response. The table below presents the  $EC_{50}$ 's of some of the compounds of the invention compared to clozapine as a reference compound.

Example #	EC <sub>50</sub> (M)
clozapine	$9.5 \times 10^0$
5j	$6.4 \times 10^{-8}$
5d	$8.4 \times 10^{-9}$
5r	$6.0 \times 10^{-9}$

**We Claim:**

1. A compound according to Formula I and salts, solvates or hydrates thereof:



wherein:

$R^1$  is selected from the group consisting of H and  $C_{1-4}$ alkyl;

$R^2$  is selected from the group consisting of H,  $C_{1-4}$ alkyl and benzyl;

$R^3$  is selected from the group consisting of  $COR^5$ ,  $SO_2R^5$ ,  $CONHC_{1-4}$ alkyl and  $C(S)SR^6$ ;

$R^{4a}$  is selected from the group consisting of H, OH, halo,  $C_{1-4}$ alkyl and  $C_{1-4}$ alkoxy;

$R^{4b}$  is selected from the group consisting of H, hydroxy, halo,  $C_{3-7}$ cycloalkyloxy,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkyl, benzyloxy, phenoxy, trifluoromethyl, trifluoromethoxy and vinyl;

$R^{4c}$  is selected from the group consisting of H, OH, halo,  $C_{1-4}$ alkyl and  $C_{1-4}$ alkoxy;

$R^{4d}$  is selected from the group consisting of H, OH, halo,  $C_{1-4}$ alkyl and  $C_{1-4}$ alkoxy;

$R^5$  is selected from the group consisting of phenyl, pyridyl, thienyl, quinoliny and naphthyl which are optionally substituted with 1-4 substituents selected

- 45 -

from C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkyl, halo, nitro, trifluoromethyl, trifluoromethoxy, 1,2-methylenedioxy, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkoxycarbonyl and C<sub>1-4</sub>alkylS-; and R<sup>6</sup> is selected from C<sub>1-4</sub>alkyl, allyl, propargyl and optionally substituted benzyl wherein the benzyl group is optionally substituted with 1-4 substituents selected from cyano, C<sub>1-4</sub>alkyl and halo.

2. A compound according to claim 1, wherein R<sup>1</sup> is methyl.
3. A compound according to claim 1, wherein R<sup>2</sup> is H.
4. A compound according to claim 1, wherein R<sup>3</sup> is selected from COR<sup>5</sup> and SO<sub>2</sub>R<sup>5</sup>.
5. A compound according to claim 4, wherein R<sup>5</sup> is selected from phenyl and thienyl optionally substituted with 1-2 groups selected from methyl, methoxy, fluoro, chloro and 1,2-methylenedioxy.
6. A compound according to claim 5, wherein R<sup>5</sup> is selected from phenyl, p-methylphenyl, p-fluorophenyl, p-methoxyphenyl, o-chlorophenyl, o-methoxyphenyl, and thienyl.
7. A compound according to claim 1, wherein R<sup>3</sup> is C(S)SR<sup>6</sup>.
8. A compound according to claim 7, wherein R<sup>6</sup> is methyl.
9. A compound according to claim 1, wherein R<sup>3</sup> is CONHmethyl.
10. A compound according to claim 1, wherein R<sup>4a</sup> and R<sup>4c</sup> are H, R<sup>4d</sup> is halo and R<sup>4b</sup> is selected from H, fluoro, cyclohexyloxy, hydroxy, benzyloxy, phenoxy, chloro and methyl.

- 46 -

11. A compound according to claim 10, wherein R<sup>4b</sup> is selected from cyclohexyloxy, chloro and fluoro and R<sup>4d</sup> is H.

12. A compound according to claim 11, wherein R<sup>1</sup> is methyl and R<sup>2</sup> is H.

13. A compound according to claim 1, which is selected from:

5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
2-Benzyl-5-hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
5-Hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
3-(1-Methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
1-(4-Methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
5-Chloro-1-(4-methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-fluorophenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-Benzoyl-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(4-Methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(4-Fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(2-Chlorobenzoyl)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(2-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(3,4-methylenedioxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(2,6-dichlorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(2-thienoyl)indole;  
1-Benzoyl-5-bromo-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-Benzoyl-5-chloro-3-(1-methyl-2-pyrrolidinylmethyl)indole;



5-Chloro-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-methylxanthyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-[S-(4-cyanobenzyl)xanthyl]indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-benzylxanthyl)indole;  
5-Methyl-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-methylxanthyl)indole;  
5-Fluoro-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-methylxanthyl)indole;  
1-(S-Benzylxanthyl)-5-fluoro-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(S-Allylxanthyl)-5-fluoro-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Fluoro-3-(1-methyl-2-pyrrolidinylmethyl)-1-(S-propargylxanthyl)indole;  
3-(1-Methyl-2-pyrrolidinylmethyl)-1-(S-methylxanthyl)indole;  
1-(S-Benzylxanthyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(S-Allylxanthyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-benzoylindole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(4-methylphenylsulfonyl)indole;  
5-Benzyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(N-methylcarboxamido)indole;  
5-Hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(N-methylcarboxamido)indole;  
1-Phenylsulfonyl-5-hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)indole; and  
1-Phenylsulfonyl-5-phenoxy-3-(1-methyl-2-pyrrolidinylmethyl)indole.

14. A compound according to claim 1, which is selected from:

5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
2-Benzyl-5-hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
5-Hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
3-(1-Methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
1-(4-Methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;

5-Chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
5-Chloro-1-(4-methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-fluorophenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-Benzoyl-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(4-Methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(4-Fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(2-Chlorobenzoyl)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(2-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(3,4-methylenedioxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(2,6-dichlorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(2-thienoyl)indole;  
1-Benzoyl-5-bromo-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-Benzoyl-5-chloro-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-benzoylindole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(4-methylphenylsulfonyl)indole;  
1-Phenylsulfonyl-5-hydroxy-3-(1-methyl-2-pyrrolidinylmethyl)indole; and  
1-Phenylsulfonyl-5-phenoxy-3-(1-methyl-2-pyrrolidinylmethyl)indole.

15. A compound according to claim 1, which is selected from:

5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
3-(1-Methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;

1-(4-Methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole;  
5-Chloro-1-(4-methoxyphenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-fluorophenylsulfonyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-Benzoyl-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(4-Methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(4-Fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(2-Chlorobenzoyl)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(2-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(2-thienoyl)indole;  
1-Benzoyl-5-bromo-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-(2-Chlorobenzoyl)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
1-Benzoyl-5-chloro-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-methoxybenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-1-(4-fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-benzoylindole;  
5-Cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)-1-(4-methylphenylsulfonyl)indole; and  
1-Phenylsulfonyl-5-phenoxy-3-(1-methyl-2-pyrrolidinylmethyl)indole.

16. A compound according to claim 1, which is selected from:

1-(2-Chlorobenzoyl)-5-cyclohexyloxy-3-(1-methyl-2-pyrrolidinylmethyl)indole;  
5-Chloro-3-(1-methyl-2-pyrrolidinylmethyl)-1-phenylsulfonylindole; and  
5-Chloro-1-(4-fluorobenzoyl)-3-(1-methyl-2-pyrrolidinylmethyl)indole.

17. A pharmaceutical composition, comprising a pharmaceutically acceptable

carrier and, in an amount effective to antagonize the 5-HT<sub>6</sub> receptor, a compound of Formula I.

18. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and, in an amount effective to antagonize the 5-HT<sub>6</sub> receptor, a compound of according to claim 13.

19. A method for treating a patient having a medical condition for which a 5-HT<sub>6</sub> receptor antagonist is indicated, comprising the step of administering to the patient a pharmaceutical composition as defined in claim 18.

20. A method for treating a patient according to claim 19, wherein the medical condition is schizophrenia.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/00222

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D403/06 A61K31/40 C07D405/14 C07D409/14 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 815 861 A (HOFFMANN LA ROCHE) 7 January 1998 see page 29 - page 30; claim 1 see page 14, line 32 - line 33 ---	1-20
P,X	WO 98 23587 A (ALLELIX BIOPHARMA) 4 June 1998 see page 27; example 5 ---	1-6, 13-15
P,X	WO 99 02493 A (WAITE DAVID CHARLES ; PFIZER LTD (GB); PFIZER (US)) 21 January 1999 see page 25, line 12 - page 26, line 2 -----	1-6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

23 June 1999

Date of mailing of the international search report

02.07.99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Fink, D

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA 99/00222

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 19 and 20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/00222

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0815861	A	07-01-1998	AU 694696 B	23-07-1998
			AU 2841697 A	22-01-1998
			BR 9703788 A	17-11-1998
			CA 2209018 A	28-12-1997
			CN 1170574 A	21-01-1998
			CZ 9702002 A	14-01-1998
			HR 970349 A	30-04-1998
			HU 9701096 A	01-02-1999
			JP 10067734 A	10-03-1998
			NO 972983 A	29-12-1997
			PL 320822 A	05-01-1998
-----				
WO 9823587	A	04-06-1998	AU 5112298 A	22-06-1998
-----				
WO 9902493	A	21-01-1999	AU 8339798 A	08-02-1999
-----				